(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 February 2002 (21.02.2002)

PCT

(10) International Publication Number
WO 02/14283 A1

(51) International Patent Classification[7]: C07D 215/227, 401/12, 257/04

(74) Agents: BRAINARD, Charles; R. et al.; Kenyon & Kenyon, One Broadway, New York, NY 10004 (US).

(21) International Application Number: PCT/US01/25398

(22) International Filing Date: 14 August 2001 (14.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/225,362 14 August 2000 (14.08.2000) US

(71) Applicant (*for all designated States except BB, US*): TEVA PHARMACEUTICAL INDUSTRIES LTD. [IL/IL]; 5 Basel Street, P.O. Box 3190, 49131 Petah (IL).

(71) Applicant (*for BB only*): TEVA PHARMACEUTICALS USA, INC. [US/US]; 1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): MENDELOVICHI, Marioara [IL/IL]; Rechov Hadar 6/12, 76466 Rehovot (IL). FINKELSTEIN, Nina [IL/IL]; 119 Harav Pardes, Apartment 16, 97350 Jerusalem (IL). PILARKSI, Gideon [IL/IL]; 12/29 Araroth, Holon (IL).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/14283 A1

(54) Title: PROCESSES FOR PREPARING CILOSTAZOL

(57) Abstract: The present invention provides processes for preparing cilostazol and processes for purifying cilostazol by recrystallization.

PROCESSES FOR PREPARING CILOSTAZOL

CROSS-REFERENCE TO RELATED APPLICATIONS

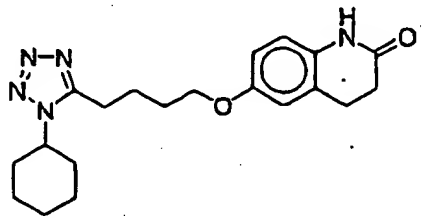
This application claims the benefit of provisional application Serial Number 60/190,588, filed March 20, 2000 and provisional application Serial Number 60/225,362, filed August 14, 2000, both of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to processes for preparing cilostazol.

BACKGROUND OF THE INVENTION

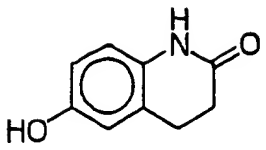
The present invention pertains to processes for preparing 6-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1*H*)-quinolinone of formula (I)



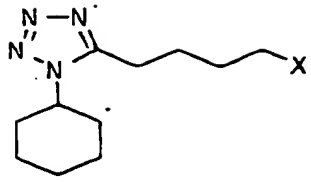
(I)

which is also known by the generic name cilostazol. Cilostazol inhibits cell platelet aggregation and is used to treat patients with intermittent claudication.

Cilostazol is described in U.S. Patent No. 4,277,479 ("the '479 patent"), which teaches a preparation wherein the phenol group of 6-hydroxy-3,4-dihydroquinolinone ("6-HQ") of formula (II) is alkylated with a 1-cyclohexyl-5-(4-halobutyl)-tetrazole ("the tetrazole") of formula (III). It is recommended to use an equimolar or excess amount up to two molar equivalents of the tetrazole (III).



(II)



(III)

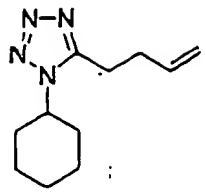
The '479 patent mentions a wide variety of bases that may be used to promote the alkylation reaction, namely, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, silver carbonate, elemental sodium, elemental potassium, sodium methylate, sodium ethylate, triethylamine, pyridine, N,N-dimethylaniline, N-methylmorpholine, 4-dimethylaminopyridine; 1,5-diaza-bicyclo[4,3,0]-non-5-ene, 1,5-diaza-bicyclo[5,4,0]-undec-7-ene ("DBU"), and 1,4-diazabicyclo[2,2,2]octane.

The '479 patent states that the alkylation may be conducted neat or in solvent. Suitable solvents are said to be methanol, ethanol, propanol, butanol, ethylene glycol, dimethyl ether, tetrahydrofuran, dioxane, monoglyme, diglyme, acetone, methylethylketone, benzene, toluene, xylene, methyl acetate, ethyl acetate, N,N-dimethylformamide, dimethylsulfoxide and hexamethylphosphoryl triamide.

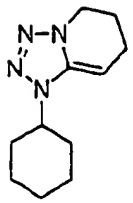
According to Examples 4 and 26 of the '479 patent, cilostazol was prepared using DBU as base and ethanol as solvent.

In Nishi, T. et al. *Chem. Pharm. Bull.* 1983, *31*, 1151-57, a preparation of cilostazol is described wherein 6-HQ is reacted with 1.2 molar equivalents of 5-(4-chlorobutyl)-1-cyclohexyl-1H-tetraazole ("CHCBT," tetrazole III wherein X=Cl) in isopropanol with potassium hydroxide as base. Cilostazol was obtained in 74% yield.

One reason for using an excess of tetrazole as was done in Nishi et al. and recommended by the '479 patent is that CHCBT is unstable to some bases. When exposed to an alkali metal hydroxide in water for a sufficient period, CHCBT undergoes elimination and cyclization to yield byproducts (IV) and (V).



(IV)



(V)

Nishi et al.'s reported yield is based upon the limiting reagent 6-HQ. The yield with respect to CHCBT is 69 %. In the economics of producing a chemical on a large scale, improvements in chemical yield are rewarded with savings in the chemical's production cost. CHCBT is an expensive compound to prepare and should not be wasted. It would be highly desirable to be able to realize further improvement in yield of the alkylation of 6-HQ with CHCBT and its halogen analogs in a way that lowers the cost of producing cilostazol. In other words, it would be desirable to further improve the yield of cilostazol by increasing the degree of conversion of CHCBT to cilostazol, as opposed to, for example, improving the yield calculated from 6-HQ by increasing the excess of tetrazole or manipulating the reaction conditions in a way that increases the conversion of 6-HQ to cilostazol but at the expense of poorer conversion of CHCBT to cilostazol.

Although CHCBT is unstable to hydroxide ion, it is relatively stable in the presence of non-nucleophilic organic bases. There are advantages to using inorganic bases, however, that favor their selection over organic bases. Firstly, the phenolic proton of 6-HQ is labile. Thus, relatively non-caustic and easily handled inorganic bases may be used to prepare cilostazol. Further, inorganic bases are easier to separate from the product and are less toxic to the environment when disposed than organic bases are. Therefore, it would also be highly desirable to use an inorganic base while realizing an improvement in conversion of CHCBT to cilostazol.

SUMMARY OF THE INVENTION

The present invention provides improved processes for preparing cilostazol (I) by alkylating the phenol group of 6-HQ with the δ carbon of a 5-(4-halobutyl)-1-cyclohexyl-1H-tetrazole.

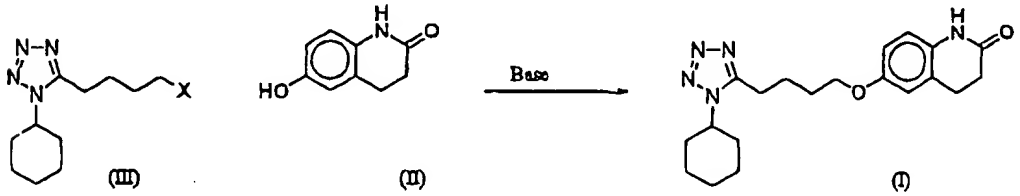
In a first aspect, the invention provides a process wherein 6-HQ and a water soluble base are dissolved in water A 1-cyclohexyl-5-(4-halobutyl)-tetrazole is dissolved in a water-immiscible organic solvent. The two solutions are combined in the presence of a quaternary ammonium salt phase transfer catalyst to form a biphasic mixture in which the 6-HQ and tetrazole react to produce cilostazol. The process may be practiced by a variety of procedures taught by the present invention. In one variation, a reaction promoter, like sodium sulfate, is added to accelerate phase transfer of 6-HQ into the organic solvent.

Another aspect of the present invention provides a preparation of cilostazol from a single phase reaction mixture of 6-HQ and a 1-cyclohexyl-5-(4-halobutyl)-tetrazole and a mixture of inorganic bases. The base mixture comprises an alkali metal hydroxide and alkali metal carbonate. This process minimizes decomposition of the starting tetrazole and cilostazol by buffering the pH which results in improved yield calculated based upon the tetrazole, the more precious of the two organic starting materials. A preferred embodiment wherein the alkali metal hydroxide is added portionwise minimizes the formation of dimeric byproducts. In another preferred embodiment of the homogeneous process, the reaction mixture is dehydrated with molecular sieves before the tetrazole is added.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a process for preparing cilostazol (I) by alkylating the phenol group of 6-HQ with the δ carbon of a 5-(4-halobutyl)-1-cyclohexyl-1H-tetrazole ("the tetrazole"). The transformation itself, depicted in Scheme 1 is known.

Scheme 1



The present invention improves upon processes previously used to perform the chemical transformation depicted in Scheme 1 which result in a greater conversion of the tetrazole starting material to cilostazol. The improvements may be viewed as falling into one of two aspects of the present invention: (1) a heterogeneous, or biphasic, process

employing phase transfer catalysis and improvements applicable to the heterogeneous process and (2) improvements applicable to a homogeneous process.

In a first aspect, the present invention provides a biphasic process for preparing cilostazol by alkylating the phenol group of 6-HQ with a 5-(4-halobutyl)-1-cyclohexyl-1H-tetrazole using controlled phase transfer methodology. For a discussion of the theory and general application of phase transfer catalysis, *See*, Dehmlow, E.V.; Dehmlow, S.S., *Phase Transfer Catalysis* 3rd ed. (VCH Publishers: New York 1993).

According to the present inventive process, a solution of 6-HQ, a water-soluble base and a trialkyl ammonium phase transfer catalyst in water is contacted with a solution of a 5-(4-halobutyl)-1-cyclohexyl-1H-tetrazole in a water-immiscible organic solvent for a period of time sufficient to cause the tetrazole to be substantially completely converted to cilostazol and then separating the cilostazol from the biphasic mixture.

The biphasic reaction mixture separates the base from the base sensitive tetrazole. Although not intending to be bound by any particular theory, it is believed that the 6-HQ phenolate anion complexes with the tetra-alkyl ammonium ion which increases its solubility in the water-immiscible organic solvent. The complexed phenolate then enters the water-immiscible phase and reacts with the tetrazole there.

Suitable phase transfer catalysts are ammonium salts such as tricaprylylmethylammonium chloride (Aliquat® 336) , tetra-n-butylammonium bromide ("TBAB"), benzyltriethylammonium chloride ("TEBA"), cetyltrimethylammonium bromide , cetylpyridinium bromide, N-benzylquininium chloride, tetra-n-butylammonium chloride, tetra-n-butylammonium hydroxide, tetra-n-butylammonium iodide, tetra-ethylammonium chloride, benzyltributylammonium bromide, benzyltriethylammonium bromide, hexadecyltriethylammonium chloride, tetramethylammonium chloride, hexadecyltrimethyl ammonium chloride, and octyltrimethylammonium chloride. More preferred phase transfer catalysts are Aliquat® 336, TBAB, TEBA and mixtures thereof, the most preferred being Aliquat® 336. The phase transfer catalyst may be used in a stoichiometric or substoichiometric amount, preferably from about 0.05 to about 0.25 equivalents with respect to the tetrazole.

Suitable bases are soluble in water but poorly soluble or insoluble in water-immiscible organic solvents. Such bases are typically metal salts of inorganic counterions. Preferred inorganic bases are hydroxide and carbonate salts of alkali metals. More preferred inorganic bases are NaOH, KOH, K_2CO_3, Na_2CO_3 and $NaHCO_3$. The most preferred inorganic base in the heterogeneous process is NaOH.

The halogen atom of 5-(4-halobutyl)-1-cyclohexyl-1H-tetrazole (X in formula III) may be chlorine, bromine or iodine, preferably chlorine. Although the tetrazole may be used in any amount desired, it is most desirable to use a stoichiometric amount of tetrazole or less relative to 6-HQ, more preferably about 0.9 molar equivalents.

Preferred water-immiscible solvents are toluene, hexanes, dichloromethane and mixtures thereof. An excess of water to water-immiscible solvent is preferred, although the ratio may vary widely. Preferred ratios of water to water-immiscible solvent range from about 0.5:1 to about 8:1 (v/v), more preferably from about 1:1 to about 6:1.

According to one preferred procedure for preparing cilostazol, the 6-HQ, water-soluble base and phase transfer catalyst are dissolved in water. The tetrazole is dissolved in the water-immiscible solvent and the two solutions are contacted and agitated, with optional heating, until the tetrazole is substantially consumed. Cilostazol may be isolated by cooling the reaction mixture to precipitate the cilostazol and then filtering or decanting the solutions. Cilostazol may be purified by methods shown in Table 1 or any conventional method known in the art.

Alternatively, a biphasic mixture of the water-miscible organic solvent and the aqueous solution of 6-HQ, water-soluble base and the phase transfer catalyst is mixed and optionally heated while the tetrazole is slowly added to the stirred mixture. The slow addition of the tetrazole may be either continuous or portionwise.

In yet another alternative procedure, an aqueous suspension of 6-HQ and the phase transfer catalyst are contacted with the solution of tetrazole in the water-immiscible organic solvent. The biphasic mixture is agitated and optionally heated; while the water-soluble base is slowly added to the mixture. The slow addition may be either continuous as in a concentrated aqueous solution of the base or portionwise.

Each of these preferred procedures may be modified to take advantage of a further improvement, which is to add a reaction promoter to the aqueous phase. Reaction promoters are salts like sodium sulfate and potassium sulfate that increase the ionic strength of aqueous solutions but do not form strongly acidic or basic aqueous solutions. The reaction promoters decrease the solubility of 6-HQ in the aqueous phase and improve the efficiency of phase transfer to the organic phase. The preferred reaction promoter is sodium sulfate. Preferably, the reaction promoter is added in the amount of about 12-16% (w/v) with respect to the aqueous phase.

In a second aspect, the present invention provides a process for preparing cilostazol by alkylating the phenol group of 6-HQ with a 5-(4-halobutyl)-1-cyclohexyl-1H-tetrazole in a single liquid phase reaction mixture. 6-HQ and the tetrazole may be used in any amount, though it is preferred that the tetrazole be the limiting reagent, preferably used in from about 0.9 to about 0.99 equivalents with respect to the 6-HQ. Suitable solvents for forming the single liquid phase reaction mixture of this aspect of the invention are non-aqueous hydroxylic solvents, which include 1-butanol, isopropanol, 2-butanol and amyl alcohol.

In this process, two inorganic bases are used to catalyze the reaction. One of the bases is an alkali metal hydroxide such as sodium or potassium hydroxide. The other base is an alkali metal carbonate such as sodium or potassium carbonate. The most preferred alkali metal is potassium. Thus, preferred base mixtures are mixtures of potassium hydroxide and potassium carbonate. The alkali metal hydroxide is preferably used in an amount of from about 0.9 to about 1.2 equivalents with respect to the 6-HQ and the alkali metal carbonate is preferably used in an amount of about 0.1 to about 0.2 equivalents with respect to the 6-HQ.

The 6-HQ, tetrazole, alkali metal hydroxide and alkali metal carbonate may be added to the non-aqueous solvent in any order desired and at any rate desired.

In one preferred procedure, 6-HQ, the tetrazole and the alkali metal carbonate are added to the hydroxylic solvent along with a portion, *e.g.* about a one-fourth portion, of the alkali metal hydroxide. Thereafter, the remainder of the alkali metal hydroxide is added portionwise to the reaction mixture. It has been found that portionwise addition of

the alkali metal hydroxide suppresses a byproduct that forms by the substitution of the halogen of the tetrazole by the 6-HQ lactam nitrogen.

Molecular sieves may be used to remove water from the single liquid phase reaction mixture before the tetrazole is added. Three and four angstrom molecular sieves are preferred, with three angstrom sieves being most preferred. The molecular sieves may be stirred with the solution to remove water formed by deprotonation of 6-HQ by KOH or adventitious water. Preferably, the molecular sieves are placed in a soxlet extraction funnel, the reservoir of a dropping funnel, or other suitable apparatus mounted on the reaction vessel that will allow circulation of vapor through the molecular sieves and return of the condensate to the reaction vessel. The solution is then refluxed to circulate water vapor over the molecular sieves. After the solution of 6-HQ phenolate has been dehydrated, the tetrazole is added to the solution to react with the 6-HQ phenolate to produce cilostazol.

In the process of Nishi et al., it was necessary to separate unreacted starting materials and the organic base by column chromatography. It is desirable in a large scale process to avoid chromatography and concomitant production of spent solid phase. We have further discovered that cilostazol prepared according to the teachings of the present invention or by other methods can be selectively crystallized from certain solvents in high purity without the need for "clean up" chromatography to remove, for example, unreacted starting materials. Suitable recrystallization solvents are 1-butanol, acetone, toluene, methyl ethyl ketone, dichloromethane, ethyl acetate, methyl t-butyl ether, dimethyl acetamide-water mixtures, THF, methanol, isopropanol, benzyl alcohol, 2-pyrrolidone, acetonitrile, Cellosolve, monoglyme, isobutyl acetate, sec-butanol, tert-butanol, DMF, chloroform, diethyl ether and mixtures thereof.

The invention will now be further illustrated with the following examples.

EXAMPLES

Example 1

Preparation of Cilostazol Using A Phase Transfer Catalyst

A 1 L reactor was charged with 6-HQ (16.5 g, 0.1011 moles), and NaOH (1 eq.) in water (90ml). To this solution was add toluene (15 ml) and CHCBT (22.22 g, 0.0915 moles), Na_2SO_4 (17 g) and catalyst (1.9 g) (aliquat 336). The mixture was heated to reflux for 8 h. After this period of time, the mixture was cooled to room temperature, the solid was filtered and washed with water and methanol to afford the crude product (29 g, yield 88%; purity by HPLC ~99%).

Example 2

Preparation of Cilostazol with Addition of CHCBT in One Portion

6-HQ (10 g, 0.0613 moles), KOH (4.05 g, 0.0722 moles), K_2CO_3 (1.5 g, 0.011 mole), CHCBT (18 g, 0.0742 moles) and n-BuOH (130 ml) were heated at reflux for ~5 hours. After cooling of the reaction mixture to room temperature the solid was filtered, washed with n-BuOH and water. The crude product (19.7 g, 85% yield) was recrystallized from n-BuOH (10 vol.) to give cilostazol crystals (yield 94%).

Example 3

Preparation of Cilostazol by Addition of The Base in Portions

6-HQ (10 g, 0.0613 moles), KOH (1.01 g, 0.018 mole), K_2CO_3 (1.5 g, 0.011 mole) , CHCBT (13.4 g, 0.0552 moles) and 130 ml n-BuOH were heated at reflux for 1hour. After 1 hour, a second 1.1 g portion of KOH was added and the reflux was continued. The procedure was repeated with two additional 1.1 g portions of KOH. After the addition of the whole KOH the reaction was continued for an additional hour. The reaction mixture was cooled to room temperature, the solid was filtered and washed with n-BuOH and dried to afford the product (15.6 g, 56 %yield).

Example 4

Preparation of Cilostazol Using Molecular Sieves as Dehydrating Agent

A three neck flask equipped with condenser and a soxlet extraction funnel containing molecular sieves 3Å (28 g) was charged with 6-HQ (10 g, 0.0613 moles) , KOH (4.05 g,

0.0722 moles) and K_2CO_3 (1.5 g, 0.011 moles) and 130 ml n-BuOH. The mixture was heated to reflux and the reflux was maintained passing the solvent over the molecular sieves. After 30 minutes, CHCBT (18 g, 0.0742 moles, 1.2 equivalents) was added and the reflux was continued for about 5h. Then, the reaction mixture was cooled and the product was filtered and washed with n-BuOH. The yield after drying was 14.4 g (62%).

Example 5

Preparation of Cilostazol Using an Excess of 6-HQ

6-HQ (10 g, 0.0613 moles), KOH (4.05 g, 0.0722 moles), K_2CO_3 (1.5 g, 0.011 mole), CHCBT (13.4 g, 0.0552 moles) and 130 ml n-BuOH were heated at reflux for 5 hours. After cooling of the reaction mixture to room temperature the solid was filtered and washed with n-BuOH and water, the material was dried to give the product cilostazol (15.93 g, 76.2% yield).

Examples 6-28

Table 1 provides conditions for selectively crystallizing cilostazol from mixtures containing minor amounts of 6-HQ and CHCBT. Cilostazol is obtained with small particle size and narrow particle size distribution.

Table 1

Example	Solvent	Volume*	Recommended Procedure
6	n-BuOH	10	
7	n-BuOH	20	
8	Acetone	20	Slurry. Reflux. Cool to r.t.
9	Toluene	20	Dissolve at reflux. Cool to r.t.
10	Methyl ethyl ketone	11	Dissolve at reflux. Cool to r.t.
11	CH_2Cl_2	4	Dissolve at reflux. Cool to r.t.
12	Ethyl acetate	10	Slurry at reflux 1h. Cool to r.t.
13	MTBE	10	Slurry at reflux 1h. Cool to r,t,
14	2:1 DMA-H2O	10	Dissolve in DMA at ~70-80°C. Add water. Cool to r.t. Precipitate at 65°C
15	THF	13	Dissolve at reflux. Cool to r.t.
16	Methanol	3	Dissolve at reflux. Cool to r.t.. Precipitate at 55°C
17	Acetone	2.5	Slurry at reflux for 1 h. Cool to r.t.
18	Ethanol	12.5	Dissolve at reflux. Cool to r.t.
19	Isopropanol	19	Dissolve at reflux. Cool to r.t.
20	Acetone	33	Dissolve at reflux. Cool to 40°C
21	Benzyl alcohol	2	Dissolve at 55°C. Cool to r.t.
22	2-Pyrrolidone	3.5	Dissolve at 65°C. Cool to r.t.
23	Acetonitrile	6.5	Dissolve at reflux. Cool to 30°C
24	2-BuOH	5	Dissolve at ~ 90°C. Cool to r.t.
25	Cellosolve	3	Dissolve at ~100°C. Cool to r.t.
26	Monoglyme	13	Dissolve at reflux. Cool to r.t.
27	iso-butyl-acetate	23	Dissolve at reflux (115°C). Cool to r.t.
28	n-BuOH	20	Dissolve at reflux. Treat with decolorizing agents, (SX1 activated carbon and tonsil silicate). Cool to r.t.

* Relative to the volume of cilostazol

It should be understood that some modification, alteration and substitution is anticipated and expected from those skilled in the art without departing from the teachings of the invention. Accordingly, it is appropriate that the following claims be construed broadly and in a manner consistent with the scope and spirit of the invention.

CLAIMS

We claim:

1. A process for preparing cilostazol comprising:
   a) dissolving 6-hydroxy-3,4-dihydroquinolinone and a water-soluble base in water to form an aqueous phase,
   b) dissolving a 1-cyclohexyl-5-(4-halobutyl)-tetrazole in a water-immiscible solvent to form an organic phase,
   c) forming a biphasic mixture by contacting the aqueous phase and the organic phase in the presence of a quaternary ammonium phase transfer catalyst,
   d) and recovering cilostazol from the biphasic mixture.
2. The process of claim 1 wherein the molar quantity of the 6-hydroxy-3,4-dihydroquinolinone is greater than the molar quantity of the 1-cyclohexyl-5-(4-halobutyl)-tetrazole.
3. The process of claim 1 wherein the water-immiscible solvent is selected from the group consisting of toluene, hexane, dichloromethane and mixtures thereof.
4. The process of claim 1 wherein the quaternary ammonium phase transfer catalyst is selected from the group consisting of tricaprylylmethylammonium chloride, tetra-n-butylammonium bromide, benzyltriethylammonium chloride, cetyltrimethylammonium bromide , cetylpyridinium bromide, N-benzylquininium chloride, tetra-n-butylammonium chloride, tetra-n-butylammonium hydroxide, tetra-n-butylammonium iodide, tetra-ethylammonium chloride, benzyltributylammonium bromide, benzyltriethylammonium bromide, hexadecyltriethylammonium chloride, tetramethylammonium chloride, hexadecyltrimethyl ammonium chloride, and octyltrimethylammonium chloride.
5. The process of claim 4 wherein the quaternary ammonium phase transfer catalyst is selected from the group consisting of tricaprylylmethyl ammonium chloride, tetrabutylammonium bromide, triethylbenzylammonium bromide and mixtures thereof.
6. The process of claim 5 wherein the quaternary ammonium phase transfer catalyst is tricaprylylmethyl ammonium chloride.

7. The process of claim 1 wherein the water-soluble base is an alkali metal hydroxide, carbonate or bicarbonate.

8. The process of claim 7 wherein the water-soluble base is selected from the group consisting of NaOH, KOH, K_2CO_3, Na_2CO_3 and $NaHCO_3$.

9. The process of claim 7 wherein the water-soluble base is NaOH.

10. The process of claim 1 further comprising dissolving a reaction promoter selected from the group consisting of potassium carbonate and sodium sulfate in the water.

11. The process of claim 1 wherein the 1-cyclohexyl-5-(4-halobutyl)-tetrazole is 1-cyclohexyl-5-(4-chlorobutyl)-tetrazole.

12. A process for preparing cilostazol comprising:

a) adding 6-hydroxy-3,4-dihydroquinolinone, a 1-cyclohexyl-5-(4-halobutyl)-tetrazole, from about 0.9 to about 1.2 equivalents of an alkali metal hydroxide with respect to the dihydroquinolinone, and from about 0.1 to about 0.2 equivalents of an alkali metal carbonate with respect to the dihydroquinolinone to a non-aqueous hydroxylic solvent to form a reaction mixture, and

b) recovering cilostazol from the reaction mixture.

13. The process of claim 12 wherein the about 0.9 to about 1.2 equivalents of alkali metal hydroxide is added in one portion.

14. The process of claim 12 wherein the alkali metal hydroxide is added by adding a first portion of the alkali metal hydroxide and after addition of the 6-hydroxy-3,4-dihydroquinolinone, 1-cyclohexyl-5-(4-halobutyl)-tetrazole, and alkali metal carbonate, adding a second portion of the alkali metal hydroxide.

15. The process of claim 14 further comprising adding a third portion of the alkali metal hydroxide after the second portion.

16. The process of claim 12 wherein the non-aqueous hydroxylic solvent is selected from the group consisting of 1-butanol, isopropanol, 2-butanol and amyl alcohol.

17. The process of claim 16 wherein the non-aqueous hydroxylic solvent is 1-butanol.

18. The process of claim 12 wherein the alkali metal hydroxide is potassium hydroxide and the alkali metal carbonate is potassium carbonate.

19. The process of claim 12 wherein the molar quantity of the 6-hydroxy-3,4-dihydroquinolinone is greater than the molar quantity of the 1-cyclohexyl-5-(4-halobutyl)-tetrazole.

20. The process of claim 12 wherein the molar quantity of the 1-cyclohexyl-5-(4-halobutyl)-tetrazole is greater than the molar quantity of the 6-hydroxy-3,4-dihydroquinolinone.

21. The process of claim 12 further comprising removing water that is formed by combining the 6-hydroxy-3,4-dihydroquinolinone and alkali metal in the hydroxylic solvent with molecular sieves.

22. The process of claim 12 wherein the 1-cyclohexyl-5-(4-halobutyl)-tetrazole is 1-cyclohexyl-5-(4-chlorobutyl)-tetrazole.

23. A process for preparing cilostazol comprising dissolving 6-hydroxy-3,4-dihydroquinolinone in a non-aqueous solvent, activating the phenol group of 6-hydroxy-3,4-dihydroquinolinone with an alkali metal hydroxide to form 6-hydroxy-3,4-dihydroquinolinone phenolate, scavenging water formed as a byproduct of the phenol activation from the solvent by entrainment in molecular sieves, and thereafter adding a 1-cyclohexyl-5-(4-halobutyl)-tetrazole and recovering cilostazol from the solvent.

24. The process of claim 23 wherein the alkali metal hydroxide is sodium hydroxide or potassium hydroxide.

25. The process of claim 23 wherein the non-aqueous solvent is selected from the group consisting of 1-butanol, toluene, hexane, dichloromethane and mixtures thereof.

26. The process of claim 23 wherein the 1-cyclohexyl-5-(4-halobutyl)-tetrazole is 1-cyclohexyl-5-(4-chlorobutyl)-tetrazole.

27. A process for purifying cilostazol by recrystallization from a solvent selected from the group consisting of 1-butanol, acetone, toluene, methyl ethyl ketone, dichloromethane, ethyl acetate, methyl t-butyl ether, dimethyl acetamide-water mixtures, THF, methanol, isopropanol, benzyl alcohol, 2-pyrrolidone, acetonitrile, Cellosolve, monoglyme, isobutyl acetate, sec-butanol, tert-butanol, DMF, chloroform diethyl ether and mixtures thereof.

28. Highly pure cilostazol free of impurities.

29. Micronized cilostazol of small particle size and narrow particle size distribution.

30. Substantially pure cilostazol prepared by the process of any of claims 1, 12 and 23.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/25398

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 215/227, 401/12, 257/04
US CL : 546/158; 548/250
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 546/158; 548/250

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- A	US 4,277,479 A (NISHI et al) 07 July 1981, column 8; column 24, Example 9.	27-30 --- 1-26
X --- A	NISHI et al. Studies on 2-oxoquinoline derivatives as blood platelet aggregation inhibitors. II. 6-[3-(1-Cyclohexyl-5-tetrazolyl)propoxy]-1,2-dihydro-2-oxoquinoline and related compounds. Chem. Pharm. Bull.1983, Vol. 31, No. 4, pages 1151-1157, especially page 1153, Chart 1; page 1154, compound VIIb and page 1156, Preparation of IVa-m and VIIa-m.	27-30 --- 1-26

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
21 November 2001 (21.11.2001)

Date of mailing of the international search report
02 JAN 2002

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703)305-3230

Authorized officer
Evelyn Huang

Telephone No. 703-308-1235

Form PCT/ISA/210 (second sheet) (July 1998)